Smith.

Synthesis Of β-β Ethylisoprophylhydroxylamine.

SYNTHESIS OF β - β - ETHYLISOPROPYL-HYDROXYLAMINE

BY

JULIAN FRANCIS SMITH

THESIS

FOR THE

DEGREE OF BACHELOR OF SCIENCE

IN

CHEMISTRY

COLLEGE OF LIBERAL ARTS AND SCIENCES

UNIVERSITY OF ILLINOIS

1916

UNIVERSITY OF ILLINOIS

May 29th, 1916

THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

Julian Francis Smith

ENTITLED Synthesis of B,B- Ethylisopropylhydroxylamine.

IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE

DEGREE OF Bachelor of Science in Chemistry

Charles Hecker
Instructor in Charge

APPROVED: W. A. Noyes

HEAD OF DEPARTMENT OF Chemistry

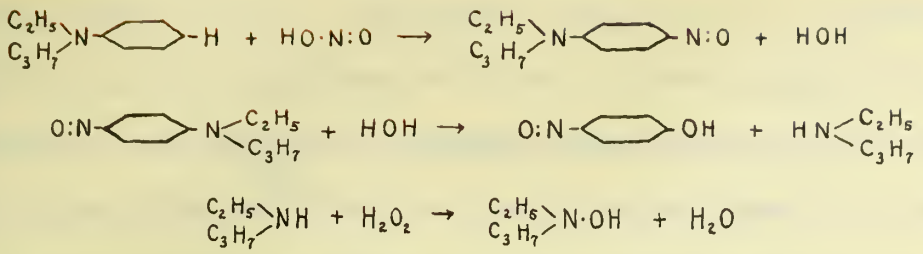
TABLE OF CONTENTS.

SYNTHESIS OF

BB- ETHYLISOPROPYLHYDROXYLAMINE.

Of the six isomeric ethylproplhydroxlamines, five had been prepared before this research was undertaken. Bewad, in 1900, obtained B,B-ethylpropylhydroxylamine as one of a number of products of the action, in ether solution, of nitromethane on zinc ethyl.[1] Later, in 1907, he prepared the same compound, together with B,B propylisoamylhydroxylamine, by treating propylmagnesium iodide with nitroethane in ether solution.[2] Four other members of the series; namely α-ethyl-β-propyl-, α-ethyl-β-isopropyl-, α-propyl-β-ethyl and α-isopropyl-β-ethylhydroxylamines, were prepared by Hecker in 1913 by hydrolysis of the corresponding carbethoxyhydroxamic esters.[3] Since it was his desire to study the electrical conductivity of the members of this series in aqueous solution, the synthesis of B,B-ethylisopropylhydroxylamine, the one remaining member, by a process different from either of the above, was undertaken under his direction.

The process chosen for the synthesis consists in the preparation, by the action of nitrous acid on ethylisopropylaniline, of p-nitrosoethylisopropylaniline, hydrolysis of this substance to p-nitrosophenol and ethylisopropylamine, and finally the oxidation of the amine thus obtained to the corresponding hydroxylamine. It was intended to study the ordinary methods of oxidation with a view to increasing the yields usually obtained in the oxidation of secondary amines. The reactions leading to the desired product may be summed up as follows:



The introduction of the nitroso group in the para position is a well known reaction of dialkyl anilines. The production of the corresponding amine by hydrolysis has also been carried out in a number of cases. Thus, dimethylamine was prepared in this manner by Baeyer and Caro in 1874,[4], and diethylamine by Norris and Kimberley in 1898[5]. The dipropylamines have not been prepared by this synthesis, nor has it been used for any higher secondary amines.

Of the mixed secondary amines, none but methylpropylamine has been synthesized by this series of reactions. It was prepared in 1896 by Stoermer and von Lepel.[6] They found that in introducing the nitroso group, the hydrochloride of the nitroso base could not be precipitated from dilute HCl solution, as in the case of compounds containing like alkyl groups, but that the precipitation proceeded nicely in concentrated HCl solution.

The final step in the series of reactions outlined above; namely, the direct oxidation of the amine thus obtained to the corresponding hydroxylamine derivative, was not attempted in any of the above cases. The subject of the direct oxidation of amines has been studied quite thoroughly, especially by Bamberger; but the present investigation is the first in which the amine to be studied was prepared as described above.

Bamberger has done much valuable work in connection with the oxidation of amines; but his researches have not been extended to

secondary alkyl amines. The direct oxidation of secondary amines having like alkyl groups was studied in 1899 by Mamlock and Wolffenstein, who prepared dipropylhydroxylamine by the action of H_2O_2 on dipropylamine.(7) Much to the disappointment of these investigators, who apparently considered this field peculiarly their own, exactly similar experiments were carried on about the same time by Dunston and Goulding, who used H_2O_2 in the oxidation of diethyl- and of dipropylamine, and reported the formation of the corresponding hydroxylamine derivatives, with about 50% yield.(8) No attempts to prepare mixed dialkylhydroxylamines by this synthesis have been reported in the literature.

If direct oxidation of mixed dialkylamines can be made to give good yields of the corresponding hydroxylamine derivatives, a considerable field is opened for the synthesis of these compounds, about which comparatively little is known. It was with this object in view that the present investigation was undertaken.

II. Experimental Part.

(a) Purification of Ethylaniline:

To obtain the ethylisopropylaniline necessary for this synthesis, ethylaniline was treated with isopropyl iodide. Crude commercial ethyl aniline was first purified by adding, slowly with cooling and stirring, 67 cc. of concentrated HCl per 100 g. of material. The hydrochloride which precipitated was filtered off with suction and pressed out thoroughly on a clay plate. Gaseous HCl was passed into the filtrate, with cooling, until another portion of the hydrochloride settled out. This second precipitate was treated like the first. The dry hydrochloride was then treated with NaOH solution, and the oil which floated to the top was drawn

off and distilled with steam. The oil thus obtained, when separated from the water layer and dried over anhydrous Na_2SO_4, boiled at 205°.5 and was evidently quite pure . Approximately two-thirds of the weight of the crude material was obtained in the pure state. This is the method of purification suggested by Blume and Kloffner.(9)

(b) Preparation of Isopropyl Iodide:

It was necessary also to prepare the required isopropyl iodide. For this purpose the well known reaction of glycerine, phosphorøus and iodine was utilized. It was found that yellow phosphorøus, with proper care in controlling the reaction, gave as good results as the red, which is usually recommended, and has the advantage of being cleaner and more convenient to work with. It was found best to carry out the reaction in a large flask under a reflux condenser, adding yellow P in pea-size lumps, waiting each time tillthe vigorous reaction had ceased before adding another. After all the phosphorøus was added, the mixture was boiled gently an hour or so under the reflux, then distilled. The product was washed free of I_2 with $Na_2S_2O_3$ solution, dried over Na_2SO_4 and distilled. The yield was always low, being slightly less than 50% of the theoretical. Of the rather copious literature on this subject, the greatest aid was derived from an article by Malbot,(10) and one by Meyer.(11)

(c) Preparation of Ethylisopropylaniline:

Ethyl aniline and isopropyl iodide, prepared and purified as above, were mixed together and heated on a gently boiling water bath under a reflux condenser for periods varying from 7 to 36 hours. Seven hours was insufficient; 15 to 18 hours gave as good results as longer periods. In one case isopropyl bromide was used instead of the iodide; after 18 hours on the water bath, it gave a yield

of 78.5% of ethyl-isopropylaniline. This was somewhat better than the yields obtained with the iodide, which lay as a rule between 70 and 75%.

In all cases, the reaction mixture solidified when the reaction was complete; the solid mass(consisting of the hydriodide or hydrobromide of ethylisopropylaniline) was dissolved in water and separated from a small amount of the unchanged mixture which floated as an oil on top. The aqueous solution was treated with NaOH, which caused the free base to separate as a pale yellow oil. This was distilled with steam, dried over anhydrous Na_2SO_4, and distilled. It boiled at 222-3°.

(d) Preparation of p-Nitrosoethylisopropylaniline:

For the introduction of the nitroso group in the para position the well known reaction of nitrous acid on dialkyl anilines was used. The first experiment was carried out in dilute solution, the ethylisopropylaniline being dissolved in a sufficient excess of HCl (1:1) to react with the nitroso base as fast as formed. The solution was cooled by surrounding it with ice and salt; then $NaNO_2$-solution was dropped in slowly, the liquid being stirred constantly during this operation. The mixture turned a deep red color, but the hydrochloride of the nitrobase did not precipitate out. An attempt to isolate it by treating the solution with KOH, extracting with ether and treating the ether solution with dry HCl yielded only a small amount of a black, sticky mass which could not be purified.

In the next experiment, the procedure recommended by Stoermer and von Lepel (12) for methylpropylaniline was followed. Finding it impossible to precipitate the salt from dilute solution, as in

the case of dimethyl- and diethylaniline, they used concentrated HCl, in approximately the proportions required to dissolve the methylpropylaniline and to form the hydrochloride of the nitroso base. The calculated quantity of $NaNO_2$ in aqueous solution was dropped in slowly, as before. But with ethylisopropylaniline this procedure gave no better results than did the first.

The next modification adoptedwas the use of alcohol in an attempt to decrease the solubility of the desired salt. Concentrated HCl, in the usual proportions, was mixed with an equal volume of alcohol (95%) for this purpose. After the $NaNO_2$- solution had been dropped in for a few minutes, a precipitate was indeed formed; but the amount was disappointingly small. On filtering with suction and washing with alcohol-ether, a bright yellow precipitate remained on the filter. Since the hydrochlorides of p-nitroso tertiary anilines reported in the literature are all bright yellow solids, this was assumed to be the desired salt. But an elementary analysis gave no test for nitrogen, and the substance was found to be non-volatile in the Bunsen flame, leaving a white solid shown by analysis to be NaCl. The yellow precipitate so painstakingly prepared evidently consisted, then, of sodium chloride colored with a small amount of the hydrochloride sought. A portion was treated with NaOH and extracted with ether; but this treatment yielded only a trace of the free base.

On account of the unexpected difficulties encountered in obtaining a precipitate, it was decided to hydrolyze the reaction mixture and isolate ethylisopropylamine from the products of hydrolysis. With this end in view, the filtrate from the NaCl precipitate was dropped slowly into a boiling dilute solution of

NaOH in a flask provided with a condenser. The distillate separated into two layers, the lower aqueous and alkaline to litmus, the upper an oil. At first the distillate was clear and colorless, but in a few minutes it had become red and turbid. The same phenomenon was observed in every subsequent attempt to obtain ethylisopropylamine in this way.

The upper layer of the distillate was separated off, dried over K_2CO_3 and distilled. It had the color and odor of ethylisopropylaniline, and boiled nicely at 221-3°. Its weight corresponded to approximately 68% of the amount used in the experiment. Herein lies at least a partial explanation of the failure to obtain a precipitate; the reaction, which proceeds so nicely with dimethyl- and diethylaniline and even with methylpropylaniline, takes place only slightly with ethylisopropylaniline.

The aqueous layer of the distillate was acidified with HCl and evaporated to dryness. The acidified solution was clear, but intensely red; the residue after evaporation, which was very small in amount in comparison to the quantity of material used in the experiment, was black and obviously impure. It was mixed with about an equal weight of dry powdered NaOH, moistened with water, and distilled. The distillate, collected over dry NaOH, was red and contained some water. It boiled rather indefinitely between 80° and 90°, and had a sharp, amine-like odor. It was evidently ethylisopropylamine, but the amount obtained was too small to permit of purification and identification.

(e) Preparation of Ethylisopropylamine by Hinsberg's Synthesis:

On account of the low yields and the difficulty of obtaining the amine in the pure state by the above method, Hinsberg's syn-

thesis for secondary alkylamines was tried. Ethylamine, treated with benzene sulphonyl chloride, splits off HCl and forms the benzene sulphonyl derivative. This compound, boiled in alkaline solution with isopropyl iodide, should yield the corresponding derivative of ethylisopropylamine. Hydrolysis should then produce ethylisopropylamine. These reactions may be summed up as follows:

$$C_2H_5NH_2 + C_6H_5SO_2Cl \rightarrow C_6H_5SO_2NHC_2H_5 + HCl$$

$$C_6H_5SO_2NHC_2H_5 + (CH_3)_2CHI \rightarrow C_6H_5SO_2N\begin{matrix}C_2H_5\\CH(CH_3)_2\end{matrix} + HI$$

$$C_6H_5SO_2N\begin{matrix}C_2H_5\\CH(CH_3)_2\end{matrix} + HOH \rightarrow C_6H_5SO_3H + HN\begin{matrix}C_2H_5\\CH(CH_3)_2\end{matrix}$$

Hinsberg (13) obtained excellent results with this process in preparing several mixed secondary aliphatic amines. Mulder, however, encountered serious difficulties when he attempted to prepare ethylisopropylamine by this method. He says, "This proves that Hinsberg's method is but poorly adapted to the synthesis of amines containing an alkyl group with a secondary C-atom."(14) A single failure seems rather meager proof for such a general statement, but the very similar failure of the synthesis first adopted for this research may be construed as lending additional support to the idea that the secondary C-atom tends to retard the reaction in question.

In spite of the low yields reported by Mulder (loc. cit.), Hinsberg's method was adopted because it was the only one for which the materials were readily available. Thirty grams of ethylamine were dissolved in a solution of 150 g. of KOH in 1100 c.c. of water cooled to 0°. To this mixture were added 176.5 g. of benzene sulphonyl chloride in small portions. The whole was allowed to stand

at room temperature for some time, and finally warmed to about 50° to remove the last portions of $C_6H_5SO_2Cl$. On acidifying this solution with HCl, an oil was precipitated, which was extracted with ether. The ether solution, when dried with Na_2SO_4 and evaporated, gave 138 g. of crystals (weighed moist). The theoretical amount is 124g. hence the yield must be quantitative. The crystals melted at 58°. A rapid control determination, by the Dumas combustion method, of the nitrogen in the impure oil before crystallization, showed N = 8.26%. The calculated N-content for $C_6H_5SO_2NHC_2H_5$ is 7.57 per cent.

The entire crystalline product was heated 6-1/2 hours on a gently boiling water bath under a reflux condenser with a mixture of 120 g. of isopropyl iodide, 40 g. KOH, about 100 cc of water and a little isopropyl alcohol. The water, isopropyl iodide and isopropyl alcohol were then distilled off, and the residue distilled in a vacuum. Nearly all of it boiled at 246-8° under 98 mm. pressure. The distillate partially solidified, leaving a pale yellow oil over white crystals of the benzene sulphonyl derivative of ethylisopropylamine. The crystals, after pressing out on a clay plate, weighed 50 g. or approximately 33% of the theoretical yield.

The white crystals were divided into three portions and hydrolyzed in sealed tubes with concentrated HCl for five hours at 150° to 170°. At the end of this time no trace of the crystals remained, and the tubes contained a clear brown liquid. As would be expected from the reaction, no gas was evolved.

The product of hydrolysis was made alkaline with NaOH and distilled into dilute HCl. The acid distillate, evaporated on the

steam bath, gave a few grams of colorless crystals which were extremely deliquescent. They melted at 79° to 85°, hence, they were a mixture. Mixed with dry NaOH and distilled, they gave a strongly alkaline distillate with a sharp, amine-like odor, whose boiling point rose gradually from about 30° to 80°. The distillate was condensed in a tube jacketed with ice-water, and collected in a receiver surrounded by a freezing mixture of ice and HCl. The liquid thus obtained, which weighed 8.4 g. was evidently a mixture of ethylamine boiling at 18°, and ethylisopropylamime, boiling at 76°. An analysis of the insoluble yellow chlorplatinate gave 38.8% as the Pt.-content. The calculated value for ethylisopropylamine chlorplatinate is 33.4%.

(f) Oxidation of Ethylisopropylamine with H_2O_2:

The amine thus obtained was oxidized with H_2O_2, using the procedure outlined by Dunstan and Goulding.(15). They allowed the solution to stand one day at room temperature, with occasional agitation. Their yields were 40 to 50%.

The H_2O_2 for these experiments was prepared by diluting Merck's Perhydrol with pure water. The amine was divided in two portions; the first was treated with 3%, the second with 6% H_2O_2. Both were allowed to stand one day at room temperature, and were shaken occasionally during this time. In both the H_2O_2 had entirely disappeared, and the odor had changed. The solutions were acidified with HCl and evaporated on a steam-bath.

The first, from 3% H_2O_2, gave a light yellow oil, about half of which crystallized on cooling. The crystalline portion was very deliquescent, and had every appearance of the hydrochloride of the unchanged amine. The oil was not noticeably deliquescent, and did

not crystallize even in a vacuum desiccator over H_2SO_4. The solid portion melted at 79 to 85°, hence, it was the hydrochloride of the original amine, and the oxidation in the 3% solution was very incomplete.

The second solution yielded only the yellow, non-crystallizable oil, the hydrochloride of the oxidized base. The oxidation was therefore much more complete with the 6% than with the 3% H_2O_2. The oily hydrochloride was poured over powdered NaOH in a small distilling bulb connected to a water-cooled condenser. There was a rapid reaction, with considerable evolution of heat. The first portion of the distillate, up to about 80°, had the sharp amine odor, then at about 120° a fraction was obtained which was of quite different character.

This substance had a peculiar, disagreeable odor, entirely different from that of the amine. It was soluble in water, alcohol and ether in all proportions and reduced Fehling's solution rather readily in the cold. In these properties it agrees quite well with its isomer, B-B-ethylpropylhydroxylamine, which boils somewhat higher, at 143-7°. The yield, while much better with 6% H_2O_2 than with the 3% solution, was somewhat less than 50%, which Dunstan and Goulding (loc. cit.1010), estimated as their yield with diethylamine and 6% H_2O_2.

III. Conclusion.

Whether or not Mulder was right in ascribing the difficulties experienced in the synthesis of ethylisopropylamine to the influence of the secondary C-atom, it must be admitted that the difficulties exist. Both the processes tried in this research can be made to lead to the formation of ethylisopropylamine, but with such poor

yields and such difficulty of thorough separation that neither is to be recommended as a method of preparation. Of the two, the method of Hinsberg gave better results; but the amount of the final product obtained was so small that no quantitative data are available.

For the oxidation of secondary amines, H_2O_2 should not be used in lower concentration than 6%, and even with such solutions the yield, after the peroxide has all reacted, is not more than half that required by theory.

In conclusion, I wish to express deep appreciation of the patient supervision and ever-ready resourcefulness of Dr. Hecker in surmounting the difficulties encountered in this research.

REFERENCES.

1. Bewad, Chem. Centralblatt (2) 945, (1900)
Journ. fur Prakt. Chem.(2) 63: 211 (1901)
2. Bewad, Ber. der Chem. Ges. 40: 3076 (1907)
3. Hecker, Am. Ch. Journ. 50: 444 (1913)
4. Baeyer and Caro, Ber. d. Chem. Ges. 7: 963 (1874)
5. Norris and Kimberley, Am. Ch. Journ. 20: 60, (1898)
6. Stoermer and von Lepel, Ber.d.Chem.Ges. 29: 2112 (1896)
7. Mamlock and Wolffenstein, Ber. d. Chem. Ges. 33: 159 (1900)
8. Dunstan and Goulding, Journ.Chem. Soc. 75: 1004 (1899)
9. Blume and Kloffner, Ber.d.Chem. Ges. 38: 3276 (1905)
10. Malbot, Ann. de Chim (6) 19: 345 (1890)
11. Meyer, Journ. fur prakt. Chem. (2) 34: 98 (1886)
12. Stoermer and von Lepel (see (6))
13. Hinsberg, Ann. der Chem. 265: 178 (1891)
14. Mulder, Rec. der Pays-bas 25: 105 (1906)
15. Dunstan and Goulding, Journ. Chem. Soc. 75: 1009, (1899)